

Acute Viral Infections with Combined Involvement of the Respiratory and Gastrointestinal Tracts in Children. Therapy with Interferon

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We evaluated the percent of acute respiratory viral infections with gastrointestinal syndrome in the structure of morbidity in babies aging 6 months and elder. Therapeutic efficiency and safety of anaferon (pediatric formulation) as a component of complex therapy of acute respiratory viral infections with involvement of the gastrointestinal tract were proven; more rapid disappearance of all symptoms and improvement of the immune status parameters were demonstrated.

Key Words: *combined involvement; respiratory tract; gastrointestinal tract; interferon inductor; immune status*

Combined involvement of the respiratory (RT) and gastrointestinal tracts (GIT) is often observed in infectious diseases, but since no differential diagnostic criteria were formulated, the diagnosis is differently defined: either as concomitant diseases, or as symptoms of GIT dysfunction in acute respiratory viral infections (ARVI), symptoms of intoxication and dysbiosis, or are not taken into account. This explains the absence of information about the contribution of ARVI with gastrointestinal syndrome in the structure of infection pathology in general and among ARVI. At the same time, a number of reports about GIT disorders in children with RT infections and catarrhal symptoms in the rhinopharynx appeared in the 1960s [4,10]. The leading role in the etiology of these disorders was played by viral infection.

Later, the development of modern methods of laboratory diagnostics and outbreaks of previously unknown infections (SARS, avian influenza, Norwalk) widened the range of viral infections that can be accompanied by acute combined involvement of

RT and GIT [6,11,12]. This complex of symptoms can be caused by either mono-infection (reproduction of the agent in epithelial cell of RT and GIT), or mixed infection (different localization of infectious agent reproduction sites) [2,8].

Taking into account the polyetiological nature of the studied pathology and early age of patients, the use of IFN preparations seems to be most promising, because these preparations have less contraindications and wider range of indications compared to chemotherapy [3]. A representative of IFN preparations, anaferon (pediatric formulation, AP), was created on the basis of ultralow doses of antibodies to IFN- γ in homeopathic dilutions C12, C30, and C50. It is widely used in the treatment of influenza and respiratory syncytial virus infection [9].

MATERIALS AND METHODS

For estimation of the percent of ARVI with gastrointestinal syndrome in the structure of ARVI, we analyzed 15,785 medical histories of children, patients of contagious isolation ward department of N. F. Filatov Children Infectious Hospital No. 5 (St. Petersburg)

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with ARVI symptoms over the period of 2003-2006 years.

Therapeutic efficiency of AP was studied in double-blind placebo-controlled randomized clinical trial including 150 children aging elder than 6 months with symptoms of acute combined involvement of RT and GIT. Of them, 100 children received the test preparation and 50 children received placebo.

AP and placebo were administered by the therapeutic scheme according to the instruction for 7-14 days depending on clinical manifestations of the disease [7]. Pathogenetically substantiated basis therapy was also given to children, when indicated.

Children of the first 3 years of life predominated in both groups (83 and 82% cases). Boys and girls constituted 55 and 45%, respectively. In most patients, the disease developed against unfavorable premorbid background, presented by manifestations of dermatological or respiratory allergosis, chronic diseases of the ear, throat, nose, and other organs, frequent acute respiratory infections, *etc.* The groups were representative by the main parameters.

For evaluation of the etiology of the disease, the routine bacteriological analysis was supplemented by complex virological tests at Laboratories of Influenza Institute, Russian Academy of Medical Sciences. Viral antigens and their nucleic acids in samples from the nasopharynx were assayed by immunofluorescence, PCR, IEA, and reaction of indirect hemagglutination, in fecal samples by IEA and transmission electron microscopy. The final step of the diagnostics was detection of increasing titers of specific antiviral antibodies in serological reactions of paired sera by the methods of inhibition and indirect hemagglutination, reaction of complement binding and IEA.

In some patients, the following immunological parameters were determined throughout the observation: total IgE content in the serum, secretory IgA in nasal washout fluid, serum, spontaneous and *in vitro* induced IFN- α and IFN- γ , and markers of immunocompetent cells CD3, CD4, CD8, CD20, and CD16 [1,5].

RESULTS

According to medical records over 4 years, combined involvement of RT and GIT was diagnosed in every 4th-5th child admitted at the hospital with ARVI symptoms (22% in 2003, 16.6% in 2004, 19.3% in 2005, and 26.2% in 2006).

In contrast to the data obtained from hospital records, where the cause of GIT dysfunction remained undetermined in 69.1% cases, employment of virological methods for patient examination drastically changed the notion about the etiological structure of the disease. Viral infection predominated in the ma-

ajority of patients: in 74-88 and 45.5-50.0% cases according to the results of the analysis of nasal and fecal samples and in 49-40% according to the results of serological studies. The cause of the disease remained undetermined in only 9% cases and in 50% cases it was presented by mixed variant with predominance of viral associations.

Adeno-, rota-, and coronavirus infections in the form of mono- or mixed variants were most prevalent (in every 3rd-4th patient). Other infections were less frequent: respiratory syncytial virus infection (21.5% cases, primarily in the form of mixed infection), influenza (15.3% cases), and norovirus and enterovirus infections.

Of bacterial agents, opportunistic flora including *Staphylococcus aureus*, *Proteus*, *Klebsiella*, and *Candida* fungi was detected in 12% cases.

In all children, the disease had a medium-severe course with acute onset and fever above 37.5°C (in 50% cases more than 38.6°C). The severity of symptoms depended on etiology. Catarrhal symptoms in the nasopharynx were most pronounced in adenoviral infection, the bronchi and lungs were involved in one-third of coronavirus infection cases. The most pronounced GIT symptoms were observed in rota- and norovirus infections. They were the main cause of exicosis in children.

Addition of AP to the basis therapy considerably reduced the duration of all symptoms of the infectious disease (Table 1). The effect of AP on the dynamics of fever reaction was most pronounced. Before the start of treatment, the structure of fever reaction was similar in both groups (body temperature rise above 38°C predominated), while one day after the start of AP treatment the number of children with high temperature significantly decreased compared to the control group, primarily due to decreased number of patients with febrile temperature. In general, in the majority of children receiving AP (81%) all symptoms of acute disease disappeared on day 5 of treatment *vs.* day 8 in the placebo group.

Addition of AP to the complex therapy led to significant increase in the level of secretory IgA, the factor of local defense, in nasal washout fluid compared to the corresponding parameter in the control group (72.6 and 32.9% cases, respectively). It can be hypothesized that activation of local immunity led to shortening of the period of secretion of viral antigen detected by immunofluorescence in nasal meatuses and, finally, to a decrease in the frequency of nosocomial infections (Fig. 1).

The disease was accompanied by changes in the content of most T cell populations, in particular, decreased content of CD3, CD4, and CD8 lymphocytes was revealed as early as during the first examination.

TABLE 1. Therapeutic Efficiency of AP in Children with Acute Combined Involvement of RT and GIT ($M\pm m$)

| Clinical symptoms | Duration of symptoms, days | |
|---------------------------------------|----------------------------|--------------------|
| | AP ($n=100$) | placebo ($n=50$) |
| Fever | 2.10±0.06* | 3.37±0.19 |
| Intoxication | 2.68±0.08* | 4.63±0.19 |
| Catarrhal symptoms in the nasopharynx | 4.33±0.10* | 6.79±0.23 |
| GIT dysfunction | 3.29±0.12* | 4.65±0.26 |
| Acute period of the disease | 4.68±0.08* | 6.78±0.22 |

Note. * $p<0.05$ compared to placebo.

On days 2-3, we observed a significant increase in the content of CD3 (primarily due to CD4 subpopulation from 34.6±1.6 to 40.1±1.3%) and CD16 (from 14.3±0.9 to 17.0±1.1%); in the placebo group these parameters decreased or remained unchanged (CD4 from 31.0±1.1 to 26.3±1.3% and CD16 (from 16.8±1.4 to 14.6±1.4%), which attested to a decrease in the number of cells participating in the formation of humoral immunity.

The induced and spontaneous production of IFN- α and IFN- γ significantly increased against the background of AP therapy compared to the control group; the total serum content of these cytokines also increased (Table 2). Moreover, despite subsequent decrease in the level of IFN to convalescence, in children receiving AP this parameter remained at a higher level.

Administration of AP induced no undesirable effects, including allergic reactions, which was con-

TABLE 2. Dynamics of the Levels of Different IFN in Children with Acute Combined Involvement of RT and GIT against the Background of AP Treatment and Placebo ($M\pm m$)

| Parameter | Time of measurement | IFN, pg/ml | |
|---|---------------------|---------------|--------------------|
| | | AP ($n=70$) | placebo ($n=26$) |
| Serum IFN- α | At admission | 44.8±2.9 | 40.8±4.5 |
| | On days 2-3 | 64.5±2.4** | 40.0±4.0 |
| | Before discharge | 48.0±2.0* | 34.8±3.8 |
| Serum IFN- γ | At admission | 59.2±2.9 | 54.4±5.1 |
| | On days 2-3 | 77.2±4.2** | 55.0±4.0 |
| | Before discharge | 58.7±3.4* | 42.5±4.0 |
| Spontaneous production of IFN- α | At admission | 75.5±3.9 | 73.3±5.6 |
| | On days 2-3 | 92.0±3.9** | 77.7±5.8 |
| | Before discharge | 66.2±2.8 | 64.0±5.1 |
| Spontaneous production of IFN- γ | At admission | 45.5±2.4 | 43.3±4.0 |
| | On days 2-3 | 63.1±2.6** | 47.5±4.5 |
| | Before discharge | 50.0±2.9 | 43.8±4.0 |
| Induced production of IFN- α | At admission | 115.0±4.8 | 127.9±0.7 |
| | On days 2-3 | 159.3±8.9** | 126.5±8.8 |
| | Before discharge | 139.0±6.3** | 104.4±5.9 |
| Induced production of IFN- γ | At admission | 91.5±5.4 | 89.8±5.6 |
| | On days 2-3 | 123.5±7.4** | 91.3±5.6 |
| | Before discharge | 101.6±4.5* | 75.4±3.0 |

Note. * $p<0.05$ compared to: *placebo, **values at admission.

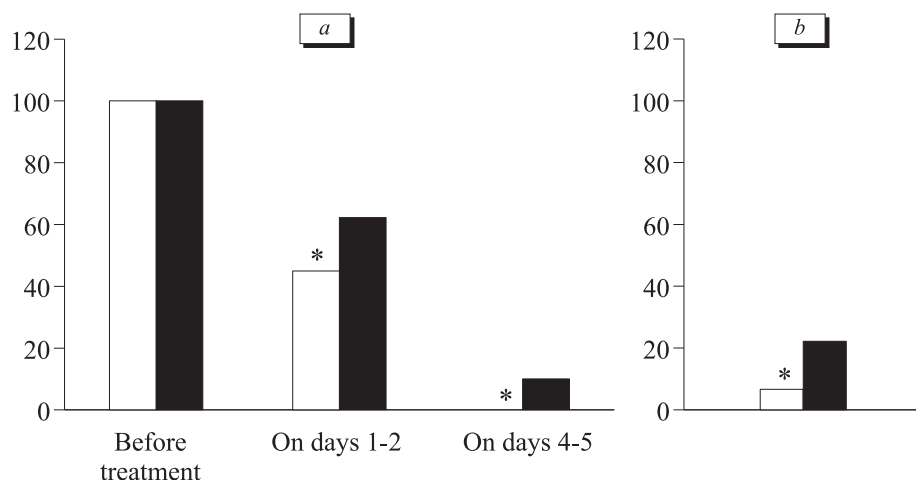


Fig. 1. Time of detection of antigens in nasal mucus (a) and incidence of nosocomial infections (b) against the background of AP treatment (light bars) and placebo (dark bars) in acute combined involvement of RT and GIT in children. * $p < 0.05$ compared to placebo.

firmly by the absence of elevated content of total IgE (and even its decrease in some cases), in contrast to that in the control group.

Thus, combined involvement of RT and GIT is recorded in every 4th-5th patient admitted to the hospital with ARVI, primarily in children of the first 3 years of life. Viral infection (adeno-, rota-, and coronavirus in the form of mono- and mixed variants) plays the leading role in the etiology of this symptom complex. The therapy should be complex and depend on the leading syndrome; IFN inductor AP can be included.

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